an iron complex dissolved in the water, the complex comprising one or more divalent or trivalent iron ions and one or more anions and having a molecular weight of less than about 50,000, the iron complex having a concentration in the water to provide an iron concentration of from about 1 to about 250 μg/dl.

31 ~~65.~~ The aqueous composition in accordance with claim 30 ~~64~~, wherein the aqueous composition is substantially hypertonic.

32 ~~66.~~ The aqueous composition in accordance with claim 30 ~~64~~, wherein the electrolytes are proportioned to prevent excessive ion removal from a patient's blood during dialysis of the blood with the composition.--

REMARKS

Reconsideration of the present application, as amended, is respectfully requested. The application, as amended, includes claims 24-29, 31-37, 39-41, 44 and 46-66, pending and under consideration.

As an initial matter, Applicant notes the above amendment to the specification, which identifies and cross-references related prior applications. Applicant claims the benefit of each identified application for purposes of priority.

The above claim amendments are presented for purposes of clarification. More specifically, the application has been amended to contain claims that recite dialysate compositions, claims that recite methods for making dialysate compositions, claims that

recite dialysate concentrate compositions and claims that recite methods for making dialysate concentrate compositions.

In the outstanding Office Action claims 40-45 are rejected under 35 U.S.C. §112, second paragraph. The Examiner states in the Action that: "The preamble recites making a dialysate (or concentrate), but the claim ends by making a 'second aqueous solution.' There is a need for some kind of a nexus between the claim preamble and the product obtained at the end of the claim so that they correspond to each other."

In reply, Applicant would point out to the Examiner that the preamble of claim 40 actually recites: "A method for making an aqueous composition useful as a dialysate." (emphasis added). Therefore, there is in these claims a nexus between the preamble and the product obtained at the end of the claim (second aqueous solution). Nevertheless, in order to moot this issue and expedite the allowance of the present case, Applicant has amended claim 40 to insert the words "useful as a dialysate." Thus, the preamble and the body of the claim, as amended and in relevant part, recite the following, respectively:

Preamble: "A method for making an aqueous composition useful as a dialysate..."

Body of Claim: "...to provide a second aqueous solution useful as a dialysate..."

In view of the above, Applicant respectfully requests withdrawal of the rejection of claims 20-45 under 35 U.S.C. §112, second paragraph.

In the outstanding Office Action, claims 24 and 26-30 are rejected "under 35 U.S.C. §102(b) as anticipated by or, in the alternative, under 35 U.S.C. §103(a) as being obvious over Mulchandani et al (U.S. 5,108,767)."

In traversal of this rejection, Applicant submits that Mulchandani et al. does not anticipate the invention of the claims, as amended, nor does it teach or suggest the claimed invention. Mulchandani et al. describes a "liquid nutritional product" (for oral ingestion) in which the "caloric distribution, vitamins and minerals, and electrolytes are carefully controlled" and in which "[t]he source of magnesium in the product is a calcium magnesium caseinate." (Abstract, Mulchandani et al.). The liquid nutritional product of Mulchandani et al.is described as addressing the unavailability of "commercially available enteral formulas designed specifically for dialysis patients" and the need for advancements in the field of "dietary management of renal patients." Table II in column 7 of Mulchandani et al., to which the Examiner refers in making this rejection, sets forth "[t]he nutrient profile of a nutritional product according to the present invention." Included in the nutrient profile of this dietary supplement is iron, which is reported to be present at a concentration of 18.9 mg/L.

Claim 24 of the present application, as amended, recites in relevant part an aqueous composition comprising water, a plurality of electrolytes, and an iron complex, the iron complex having a concentration in the water to provide an iron concentration of from about 1 to about 250 μg/dl. Each of claims 26-30 depends directly or indirectly from claim 24. Applicant notes that original claim 31 is not rejected in the outstanding Office Action over Mulchandani et al. As the subject matter of original claim 31 is now recited in claim 24, as amended, Applicant submits that the rejection of claims 24 and 26-30 should be withdrawn for the same reasons that original claim 31 was not rejected over this reference.

In addition, Applicant submits that the concentration of iron in Mulchandani et al. (18.9mg/L) is almost eight times greater than the iron concentration recited in claims 24-30, as amended (i.e., "from about 1 to about 250 μg/dl"). Because Mulchandani et al. does not describe an aqueous composition as recited in claims 24 and 26-30, as amended, having an iron concentration of from about 1 to about 250 μg/dl, Applicant submits that the rejection of these claims under 35 U.S.C. §102(b) must be withdrawn.

Applicant would also draw the Examiner's attention to new claims 46-53 drawn to more concentrated aqueous compositions "wherein the electrolytes and the iron complex have concentrations in the water whereby the composition is effective for dilution to provide a dialysate having an electrolyte concentration of from about 223 mEq/L to about 323 mEq/L and an iron concentration of from about 1 to about 250 μg/dl." In a more concentrated aqueous composition as recited in these claims, commonly termed a dialysate concentrate, the proportions of electrolytes to iron are such that the concentrate can be diluted to provide a suitable dialysate composition. Mulchandani et al. does not anticipate these claims because it does not disclose a composition having the recited elements in the recited proportions. For the above reasons, the presently claimed invention is not anticipated by Mulchandani et al.

In addition, Applicant submits that the claimed invention is not obvious in view of Mulchandani et al. because Mulchandani et al. provides no teaching, suggestion or motivation to practice the presently claimed invention. As noted above, Mulchandani et al. discloses a dietary nutritional supplement, formulated to be orally ingested, which is an entirely different type of composition than the dialysate and dialysate concentrate

compositions disclosed and claimed in the present application. Using this oral nutritional supplement as a dialysate would be deadly, at least due to the electrolyte concentrations recited therein. The importance of electrolytes in a dialysate composition is well known. Electrolytes in the dialysate function to maintain electrolyte stability in blood during dialysis. The dietary supplement described in Mulchandani et al. includes 36 mEq/L of sodium, which is about one fourth of the level of sodium typically in a patient's blood. Thus, using this composition as a dialysate would at the very least result in a fatal loss of body sodium. Furthermore, the described dietary supplement includes 27 mEq/L of potassium, which is about six times greater than the level of potassium typically in a patient's blood. Thus, using this composition as a dialysate would also at the very least result in fatal potassium elevation. Applicant does not dispute that the prior art includes a variety of products designed to supplement iron in a person's diet; however, Applicant submits that information regarding dietary iron supplementation does not in any manner teach or suggest the present invention.

To establish a *prima facie* case of obviousness, the Examiner must identify in the prior art some teaching, suggestion or motivation to modify the cited reference. "Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art." (citations omitted). Manual of Patent Examining Procedure ("MPEP") §2143.01. Some teaching in the prior art as a whole must suggest the desirability, and thus the obviousness, of making the

combination. Lindemann Maschinenfabrik GmbH v. American Hoist and Derrick Co., 221 U.S.P.Q. 481, 488 (Fed. Cir. 1984). In addition, section 2142 of the Manual of Patent Examining Procedure ("MPEP") states that:

> The initial burden is on the examiner to provide some suggestion of the desirability of doing what the inventor has done. 'To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references.' (citation omitted)."

Applicant submits that there is no teaching or suggestion in this reference or in the known prior art to modify an oral nutritional dietary supplement in a manner to make it suitable for use as a dialysate or a dialysate concentrate as claimed in the present application, as amended.

As noted previously in the record of this case, the specification of the present application describes at great length the problems in the prior art associated with the delivery of iron to patients, which problems are addressed by the invention in a unique manner. There is no teaching, suggestion or motivation found in Mulchandani et al. to incorporate inventive iron complexes into a dialysate to achieve iron delivery during dialysis. For these reasons, and also because the subject matter of original claim 31 has been incorporated into claim 24, as amended, Applicant requests withdrawal of all rejections based upon Mulchandani et al.

In the outstanding Office Action, claims 24-45 are rejected "under 35 U.S.C. §103(a) as being unpatentable over Bellini et al (EP 612,528) in view of the acknowledged prior art and Martindale The Extra Pharmacopoeia." In the Office Action, the Examiner lists the following as providing the basis for this rejection:

(1) "Bellini et al. disclose solutions for peritoneal dialysis that contain electrolytes (at the milliequivalent range required in the instant claims), gluconate salt such as iron gluconate and glucose." (Page 3).

(2) Iron deficiency is commonly encountered in pregnancy and in various disease states such as end stage renal disease. (Applicant's specification, page 2).

(3) Chronic dialysis patients often require iron supplementation. (Action, page 4).

(4) Oral iron supplementation with substances such as ferrous gluconate, ferrous citrate, ferrous sulfate, ferrous fumarate, and ferric polysaccharide complexes is known. (Applicant's specification, page 3).

(5) Intraperitoneal delivery of iron dextran is known. (Applicant's specification, page 3).

(6) Ferrous fumarate, ferrous gluconate, ferrous succinate, ferrous sulfate and ferrous gluconate + calcium are known for treating iron deficiency. (Martindale).

The Examiner then concludes that:

> Bellini's dialysate formulation may contain ferrous gluconate. Given the known use of ferrous gluconate and other iron compound in oral iron supplementation, taken with the known intraperitoneal delivery of an iron substance, one having ordinary skill in the art would have been particularly motivated to utilize ferrous gluconate as the gluconate species in Bellini's dialysate formulation to treat dialysis patients who are in need of iron supplementation.

(Office Action, Page 4).

With respect to item 5 above, Applicant notes again that the present application claims priority to a U.S. Provisional Application filed prior to the date of this reference; however, this information would not in any event provide any teaching or suggestion to a person of ordinary skill in the art to practice the presently claimed invention due to the widespread belief that soluble iron would be toxic if it were to be contacted with blood, discussed more fully below.

With respect to items 2, 4 and 6 above, Applicant submits that the existence of patients having iron requirements and the existence of a variety of oral iron supplements currently available provide no teaching, suggestion or motivation relevant to the present invention, which relates to novel compositions and methods relating to the delivery of iron to a patient via dialysis. The continuing need of iron delivery to various patients has been the subject of much research over many decades and continues to present a significant problem, even though improved oral iron supplements have been developed.

With respect to the newly cited Bellini et al. reference, Applicant submits that this reference also does not provide a teaching, suggestion or motivation to practice the claimed invention. Applicant submits that Bellini et al. cannot be cited as teaching or suggesting a dialysate formulation that contains ferrous gluconate because Bellini et al. would not motivate a person of ordinary skill in the art to include ferrous gluconate in a dialysate. Indeed, Bellini et al. does not teach the presence of ferrous gluconate in a peritoneal dialysate as it might appear and as the Examiner has asserted. Bellini et al. discloses "solutions for peritoneal dialysis that contain an osmotic substance with is an alternative to glucose." (Col. 1, lines 1-3). More specifically, Bellini et al. disclose "a peritoneal dialysis solution ...characterized in that it comprises an osmotic substance chosen among gluconic acid and its pharmaceutically acceptable salts." (Col. 2, lines 30-34). Bellini et al. also separately recites a "laundry list" of gluconic acid salts, including calcium gluconate, zinc gluconate, sodium gluconate, sodium stibogluconate, magnesium gluconate and iron gluconate (Col. 2, line57 through Col 3, line 1).

Although Bellini et al. discloses (1) the use of gluconic acid or a salt thereof as an osmotic substance and (2) that a "laundry list" of known gluconic acid salts includes iron gluconate, this reference does not teach or enable a peritoneal dialysis protocol using a dialysate including iron gluconate, and would not motivate a person of ordinary skill in the art to include iron gluconate in a dialysate.

Bellini et al. states that: "Advantageously, gluconic acid and/or any salts thereof are included in the peritoneal dialysis solution according to the present invention at a concentration of 1 to 5% by weight and therefore of 10 g/l up to 50 g/l." (Col. 2, lines 38-42). If iron gluconate were selected as the gluconic acid salt in Bellini et al., as suggested by the Examiner, the dialysate would include from 10 g/l up to 50 g/l of iron gluconate, which would equal from about 91,000 to about 455,000 μg/dl of iron in the peritoneal dialysate. While the Bellini et al. dialysate may have good osmotic properties by virtue of a gluconic acid salt, Applicant submits that a person of ordinary skill in the art would not read Bellini et al. as teaching or suggesting the inclusion of ferrous gluconate in a dialysate. Rather, a person of ordinary skill in the art would dismiss any notion of including ferrous gluconate as the source of the gluconate salt, concluding that a peritoneal dialysate including ferrous gluconate, especially from about 91,000 to about 455,000 μg/dl of iron from ferrous gluconate, would be toxic.

The specification of the present application describes at great length the problems in the prior art associated with the delivery of iron to patients, which problems are addressed by the invention in a unique manner. Prior to the present invention, however, there was no teaching, suggestion or motivation to incorporate inventive iron complexes

into a dialysate to achieve iron delivery during dialysis and the prior art teaches away from such incorporation. The combination of an inventive iron complex and a dialysate has historically been considered extremely dangerous. As stated at page 7 of the present application, "it is widely believed that soluble iron complexes are unacceptable iron delivery agents, this belief being based upon a fear of the toxicity of free iron in blood." (Specification, page 7, lines 5-8). Because of this widespread belief, the prior art would motivate a skilled artisan to ensure that an inventive iron complex is not administered to a patient in such a way that the complex would be transported to the patient's blood, such as, for example, via dialysis. Thus, the prior art teaches away from incorporating an iron complex in accordance with the present invention into a dialysate.

It appears that, when compiling a "laundry list" of gluconic acid salts, Bellini et al. simply did not consider the physiologic effects of including iron gluconate in a dialysate. Because Bellini et al. provide no experimental data reporting tests of a dialysate having such high concentrations of iron, and because Bellini et al. provide no further guidance regarding the selection of a gluconic acid salt from the recited listed, Applicant submits that Bellini et al. does not provide an enabling disclosure of a dialysate including ferrous gluconate.

Furthermore, if ferrous gluconate were selected from the laundry list and included in a dialysate in the concentrations described in the Action, the lower end of the Bellini et al. range would provide a concentration of iron that is more than 300 times greater than the iron concentrations in dialysate concentrates described and claimed in the present application, as amended. Bellini et al. does not teach or suggest a dialysate having a

concentration of an iron complex as described and claimed in the present application, and Bellini et al. would not motivate a person of ordinary skill in the art to modify the disclosure to arrive at the presently claimed invention.

As stated above, to establish a *prima facie* case of obviousness, the Examiner must identify in the prior art some teaching, suggestion or motivation to combine or modify the cited references. "Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art." (citations omitted). Manual of Patent Examining Procedure ("MPEP") §2143.01. In addition, the prior art reference (or references, when combined) must teach or suggest all the claim limitations (See MPEP §2142)

It is respectfully submitted that there is no contemplation of the present invention in Bellini et al. and that there is no teaching, suggestion or motivation in the prior art of a composition including the limitations recited in the pending claims, as amended. Applicant further submits that the prior art teaches away from the present invention for the reasons previously stated. Therefore, Applicant respectfully submits that the claims are allowable over the references of record and requests that the rejection under 35 U.S.C. §103 in view of Bellini et al. be withdrawn.

In the outstanding Office Action, claims 24-45 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 5,906,978. Enclosed herewith is a Terminal Disclaimer,

executed by an official authorized to sign such documents for Makoff R&D Laboratories, Inc., the owner of the present application and U.S. Patent No. 5,906,978. In view of this Terminal Disclaimer, Applicant submits that this rejection is overcome.

For the reasons stated herein, Applicant submits that the present application, as amended and containing claims 24-29, 31-37, 39-41, 44 and 46-66, is in condition for allowance. Action to that end is therefore respectfully solicited.

Respectfully submitted

By: _____

Gregory B. Coy
Reg. No. 40,967
Woodard, Emhardt, Naughton,
Moriarty & McNett
Bank One Center/Tower
111 Monument Circle, Suite 3700
Indianapolis, Indiana 46204-5137
(317) 634-3456

37011-6:GBC:101347